General

Guideline Title

Schizophrenia.

Bibliographic Source(s)

Singapore Ministry of Health. Schizophrenia. Singapore: Singapore Ministry of Health; 2011 Jul. 48 p. [107 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Singapore Ministry of Health. Schizophrenia. Singapore: Singapore Ministry of Health; 2003 Feb. 40 p.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 10, 2016 – Olanzapine : The U.S. Food and Drug Administration (FDA) is warning that the antipsychotic medicine olanzapine can cause a rare but serious skin reaction that can progress to affect other parts of the body. FDA is adding a new warning to the drug labels for all olanzapine-containing products that describes this severe condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- May 3, 2016 – Aripiprazole (Abilify, Abilify Maintena, Aristada) : The U.S. Food and Drug Administration (FDA) is warning that compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex have been reported with the use of the antipsychotic drug aripiprazole (Abilify, Abilify Maintena, Aristada, and generics). These uncontrollable urges were reported to have stopped when the medicine was discontinued or the dose was reduced. These impulse-control problems are rare, but they may result in harm to the patient and others if not recognized.

Recommendations

Major Recommendations

Definitions of the level of evidence (1++, 1+, 1-, 2++, 2+, 2-, 3, 4) and the grades of recommendations (A, B, C, D, GPP) are defined at the end

of the "Major Recommendations" field.

Treatment of Acute Symptoms

GPP - The preliminary step in management involves establishing diagnosis and ruling out psychoses that could be secondary to physical morbidity or substance use. The patient's social supports, functioning and relative risk of self-harm or harm to others must be evaluated for choice of treatment setting. (GPP)

A - People newly diagnosed with schizophrenia should be offered oral antipsychotic medication. (Grade A, Level 1++)

GPP - Clinicians must provide information and discuss the benefits and side-effect profile of each drug with the patient. (GPP)

A - The recommended optimal oral dose of antipsychotic is 300-1000 mg chlorpromazine equivalents daily for an adequate duration of 4-6 weeks. Treatment should be started at the lower end of the licensed dosage range and slowly titrated upwards (refer to table in Annex II in the original guideline document). (Grade A, Level 1++)

D - If there is inadequate response by 4-6 weeks or if patient develops intolerable side effects, the medication should be reviewed and another typical or an atypical antipsychotic should be used (refer to the algorithm in Annex II in the original guideline document). (Grade D, Level 4)

A - Oral antipsychotics should be used as first-line treatment for patients with an acute relapse of schizophrenia. (Grade A, Level 1++)

GPP - Choice of antipsychotic should take into account the patient's previous treatment response, side effect experience, co-morbid conditions, compliance history and preference. (GPP)

Maintenance Pharmacotherapy

A - For maintenance therapy, antipsychotic dose should be reduced gradually to the lowest possible effective dose, which should not be lower than half of the effective dose during the acute phase. (Grade A, Level 1+)

B - Combination of antipsychotics is not recommended except during transitional periods when patients are being switched from one antipsychotic to another, or when used for clozapine augmentation (see Annex II in the original guideline document). (Grade B, Level 2++)

C - Long-acting depot antipsychotics may be indicated in patients in whom treatment adherence is an issue or when a patient expresses a preference for such treatment. (Grade C, Level 2+)

B - Long-acting depot antipsychotics should not be used for acute episodes because it may take 3-6 months for the medications to reach a stable steady state. (Grade B, Level 2++)

C - Patients receiving atypical antipsychotics should be regularly monitored for metabolic side effects (refer to Annex III in the original guideline document). (Grade C, Level 4)

Management of Treatment-resistant Schizophrenia

A - Clozapine should be offered to patients whose illness has not responded adequately to treatment despite the sequential use of adequate doses and duration of at least two different antipsychotics. (Grade A, Level 1++)

GPP - For all patients on clozapine, clinicians should have their full blood count monitored weekly for the first 18 weeks and monthly thereafter. (GPP)

D - Electroconvulsive therapy should be considered for patients who have not responded to an adequate trial of antipsychotics and patients with life threatening symptoms such as catatonia and prominent depressive symptoms. (Grade D, Level 3)

A - Electroconvulsive therapy should not be prescribed as first line treatment or monotherapy in schizophrenia. (Grade A, Level 1+)

Adjunctive Medications

A - Antidepressants should be considered when depressive symptoms emerge during the stable phase of schizophrenia (post-psychotic depression). (Grade A, Level 1+)

D - Antidepressants should be used at the same dose as for treatment of major depressive disorder. (Grade D, Level 4)

A - Anticholinergic agents have been shown to be effective in reducing the severity of antipsychotic-induced extrapyramidal side effects and may be prescribed to patients experiencing these side effects. (Grade A, Level 1+)

Psychosocial Interventions

GPP - Psychosocial interventions should be tailored to the needs of the patients. (GPP)

A - Patients and their family members should be educated about the illness, its course, and prognosis as well as the efficacy of the various medications, the anticipated side effects and costs. Family interventions should also incorporate support, problem-solving training and crisis-intervention. (Grade A, Level 1+)

A - Early psycho-education and family intervention should be offered to patients with schizophrenia and their families. (Grade A, Level 1+)

B - Sheltered, transitional or supported employment should be offered to patients with schizophrenia as part of a psychiatric rehabilitation programme to enhance their vocational skills. (Grade B, Level 2++)

A - Cognitive remediation may be considered to improve attention, memory and executive function among people with schizophrenia. (Grade A, Level 1+)

A - Cognitive remediation should be provided by occupational therapists within the framework of a psychiatric rehabilitation programme, with a functional goal in mind. (Grade A, Level 1+)

A - Psychological therapy, in particular cognitive behaviour therapy (CBT), administered in combination with routine care should be considered for patients with schizophrenia, particularly those with persistent negative and positive symptoms. (Grade A, Level 1+)

A - Assertive community treatment should be recommended for patients with high rates of hospitalizations as well as for those patients with a high potential for homelessness. (Grade A, Level 1+)

Pregnancy

D - Treatment options for schizophrenia patients who are pregnant should be individualised, with consideration of severity of previous episodes, duration of remission since last episode, response to treatment and the woman's preference after full and informed discussion. (Grade D, Level 4)

GPP - Schizophrenia patients who are pregnant should be referred for urgent specialist consultation if they have not been seen by a specialist before. (GPP)

GPP - Abrupt cessation of medications should be avoided in schizophrenia patients who are pregnant as it can increase the risk of relapse, particularly in the early weeks of pregnancy when hormonal changes make the woman more vulnerable. (GPP)

D - Healthcare providers should provide psychoeducation to women with schizophrenia in the childbearing age-group on the risk considerations in pregnancy and counsel patients on family planning and sexuality issues as is appropriate. (Grade D, Level 4)

Definitions:

Levels of Evidence

Level	Type of Evidence
1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g., case reports, case series
4	Expert opinion

Grades of Recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of randomised controlled trials (RCTs), or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group

Clinical Algorithm(s)

A medication algorithm for schizophrenia is provided in the original guideline document.

Scope

Disease/Condition(s)

Schizophrenia

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Psychiatry

Psychology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Nurses

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Social Workers

Guideline Objective(s)

To provide information to clinicians on the evidenced-based treatment for schizophrenia

Target Population

Adults with schizophrenia

Note: These guidelines do not cover management of other psychotic disorders like brief psychotic disorders, schizoaffective disorders, bipolar disorders with psychotic symptoms or delusional disorders.

Interventions and Practices Considered

Assessment/Evaluation

1. Assessment of patient for symptoms of schizophrenia, co-morbid psychiatric illness, co-morbid medical condition, or substance abuse
2. Evaluation of patient's social supports, functioning, and relative risk of self-harm or harm to others

Treatment

1. Pharmacotherapy
    - Antipsychotic medications (trifluoperazine, chlorpromazine, aripiprazole, paliperidone, perphenazine, ziprasidone, haloperidol, sulpiride, clozapine, risperidone, olanzapine, quetiapine, amisulpride)
    - Depot antipsychotic medications
    - Maintenance and discontinuation of antipsychotics
    - Adjunctive medications, including anticholinergic agents and antidepressants
    - Monitoring of response to medications and adjustments as necessary
2. Electroconvulsive therapy (ECT)
3. Psychosocial interventions
    - Psychoeducation/family intervention
    - Psychiatric rehabilitation programme
    - Cognitive remediation
    - Psychological intervention
    - Assertive community treatment
4. Management of pregnant women and women of childbearing age

Major Outcomes Considered

- Effectiveness of medications
- Side effects, adverse effects, and costs of treatment
- Rates of relapse, coping skills, social and vocational functioning, and ability to function independently
- Decrease in psychiatric symptoms

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Searches were run on PubMed (1966-2010); EMBASE (1947-2010), the Cumulative Index to Nursing & Allied Health (CINAHL) database (1984-2010) and PsycINFO (1806-2010) for searching evidence related to schizophrenia. Additionally both the Cochrane Library (2011, Issue 1) and Centre for Reviews and Dissemination databases (DARE, NHS EED and HTA) were searched for systematic reviews and cost effectiveness studies. The guideline developers also performed Internet search on websites of guidelines agencies and professional societies that published clinical practice guidelines and consensus evidence on the given condition. These include the search for the last five years of the existing clinical practice guidelines (2006-2010) from sources of overseas guidelines agencies and professional bodies, e.g., National Guideline Clearinghouse, National Health Service (NHS) National Library of Guidelines, the Guidelines International Network, Agency for Healthcare Research and Quality (AHRQ), Canadian Medical Association (CMA) Clinical Practice Guidelines, New Zealand Guidelines Group, Australia's Clinical Practice Guidelines Portal websites.

Inclusion/exclusion criteria were used specific to the clinical questions to be answered. In general, search filters were used to further focus the type of studies to randomised controlled trials and systematic reviews of randomised controlled trials. If there is a paucity of higher level evidence, lower level evidence may be considered.

All searches used keywords and MeSH headings or the controlled vocabulary specific to the databases for the condition specified.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

Level	Type of Evidence
1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g., case reports, case series
4	Expert opinion

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This guideline was developed by a multidisciplinary workgroup appointed by the Ministry of Health, Singapore. The workgroup consisted of a family practitioner, a family therapist, a healthcare administrator, occupational therapists, a patient advocate, pharmacists, psychiatrists and psychologists.

This guideline was developed by reviewing relevant literature, adapting existing guidelines and by expert clinical consensus with consideration of local practice.

Rating Scheme for the Strength of the Recommendations

Grades of Recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of randomised controlled trials (RCTs), or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group

Cost Analysis

See Section 8 of the original guideline document for a discussion of cost-effectiveness issues.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate evaluation and management of schizophrenia

Potential Harms

Common Side Effects of Antipsychotic Medications

- Sedation
- Anticholinergic side effects, e.g., dry mouth, dry eyes, blurred vision, urinary complaints and constipation
- Antiadrenergic side effects, e.g., postural hypotension, delayed ejaculation
- Weight gain
- Transaminitis
- Cardiovascular side effects include electrocardiogram (ECG) changes, e.g., prolonged QTc, cardiac arrhythmias
- Lowered seizure threshold

Common Side Effects of Typical Antipsychotic Medications

- Extrapyramidal side effects, e.g., dystonia, akathisia, parkinsonism
- Tardive dyskinesia
- Hyperprolactinemia (amenorrhoea, galactorrhoea and breast enlargement in females, and impotence and gynaecomastia in males)
- Neuroleptic malignant syndrome

Common Side Effects of Specific Atypical Antipsychotic Medications

- Risperidone: rhinorrhoea, blocked nose and at higher dosages, the side effect profile is similar to typical antipsychotic medications with increased extrapyramidal side effects and hyperprolactinemia
- Olanzapine: sedation, weight gain, postural hypotension and anticholinergic side effects
- Quetiapine: sedation, postural hypotension, anticholinergic side effects
- Aripiprazole: headaches, insomnia and anxiety
- Ziprasidone: drowsiness, anxiety and arrhythmias

Abrupt cessation of medications should be avoided in schizophrenia patients who are pregnant as it can increase the risk of relapse, particularly in the early weeks of pregnancy when hormonal changes make the woman more vulnerable.

Qualifying Statements

Qualifying Statements

- These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.
- The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.
- Evidence-based guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supercede recommendations in this guideline. The workgroup advises that this guideline be scheduled for review five years after publication, or when new evidence appears that requires substantive changes to the recommendations made in this guideline.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Singapore Ministry of Health. Schizophrenia. Singapore: Singapore Ministry of Health; 2011 Jul. 48 p. [107 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2003 Feb (revised 2011 Jul)

Guideline Developer(s)

Singapore Ministry of Health - National Government Agency [Non-U.S.]

Source(s) of Funding

Singapore Ministry of Health

Guideline Committee

Workgroup on Schizophrenia

Composition of Group That Authored the Guideline

Workgroup Members: A/Prof Swapna Verma (*Chairman*), Chief & Senior Consultant, Department of Early Psychosis Intervention Programme, Institute of Mental Health; Ms Chan Lay Lin, Principal Medical Social Worker, Medical Social Work Department, Institute of Mental Health; Mr Chee Kok Seng, Principal Clinical Pharmacist, Community Wellness Centre; Dr Chen Yu, Helen, Head & Senior Consultant Psychiatrist, Mental Wellness Service, KK Women's & Children's Hospital; Dr Chin Swee Aun, Deputy Director (Primary Care), Primary and Community Care Division, Ministry of Health (till 3 Jan 2011); A/Prof Chong Siow Ann, Vice-Chairman Medical Board (Research), Institute of Mental Health; Ms Chua Pei Ling, Wendy, Senior Occupational Therapist, Institute of Mental Health; A/Prof Calvin Fones Soon Leng, Senior Consultant Psychiatrist, Fones Clinic-Psychological Medicine, Gleneagles Medical Centre; A/Prof Fung Shuen Sheng, Daniel, Vice-Chairman Medical Board (Clinical) & Senior Consultant, Department of Child & Adolescent Psychiatry, Institute of Mental Health; Adj A/Prof Sim Kang, Senior Consultant, Department of Psychiatry, Institute of Mental Health; Ms Khoo Chai Ling, Senior Pharmacist, Pharmacy Department, Institute of Mental Health; Dr Kwek Seow Khee, Daniel, Senior Consultant, Department of Medicine, Alexandra Hospital; Ms Joycelyn Ling, Senior Psychologist, Department of Early Psychosis Intervention Programme, Institute of Mental Health; Ms Porsche Poh, Executive Director, Silver Ribbon (Singapore), Board Director, World Federation for Mental Health; Ms Tan Bhing Leet, Head of Occupational Therapy Department, Institute of Mental Health; Dr Tan Yong Hui, Colin, Senior Family Physician, Assistant Director, Clinical Services, National Healthcare Group Polyclinics; A/Prof Tan Lay Ling, Senior Consultant, Department of Psychological Medicine, Changi General Hospital; A/Prof Tan Chay Hoon, Visiting Consultant, Department of Psychological Medicine, National University Hospital, Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore; Adj Assistant Prof Tay Woo Kheng, Senior Consultant, Department of Psychological Medicine, Changi General Hospital

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Singapore Ministry of Health. Schizophrenia. Singapore: Singapore Ministry of Health; 2003 Feb. 40 p.

Guideline Availability

Electronic copies: Available from the Singapore Ministry of Health Web site .

Print copies: Available from the Singapore Ministry of Health, College of Medicine Building, Mezzanine Floor 16 College Rd, Singapore 169854.

Availability of Companion Documents

The following are available:

- Schizophrenia. Executive summary of recommendations. Singapore: Singapore Ministry of Health; 2011 Apr. 8 p. Electronic copies: Available in Portable Document Format (PDF) from the Singapore Ministry of Health Web site .
- Schizophrenia and depression in the peripartum. Slide presentation. 23 p. Electronic copies: Available in PDF from the Singapore Ministry of Health Web site .
- Pharmacological interventions in schizophrenia. Slide presentation and videos. Available from the Singapore Ministry of Health Web site .
- Role of voluntary welfare organisations in community management of schizophrenia. Slide presentation and videos. Available from the Singapore Ministry of Health Web site .

Self-assessment questions and clinical quality improvement parameters are also available in the original guideline document .

Patient Resources

None available

NGC Status

This summary was completed by ECRI on November 28, 2003. This summary was updated by ECRI on January 18, 2006, following the U.S. Food and Drug Administration advisory on Clozaril (clozapine). This summary was updated by ECRI Institute on October 2, 2007, following the U.S. Food and Drug Administration (FDA) advisory on Haloperidol. This summary was updated by ECRI Institute on November 6, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs. This summary was updated by ECRI Institute on January 10, 2008, following the U.S. Food and Drug Administration advisory on Carbamazepine. This NGC summary was updated on March 15, 2013. This summary was updated by ECRI Institute on December 18, 2014 following the U.S. Food and Drug Administration advisory on Ziprasidone. This summary was updated by ECRI Institute on October, 5 2015 following the U.S. Food and Drug Administration advisory on Clozapine. This summary was updated by ECRI Institute on May 24, 2016 following the U.S. Food and Drug Administration advisory on Olanzapine. This summary was updated by ECRI Institute on May 31, 2016 following the U.S. Food and Drug Administration advisory on Aripiprazole (Abilify, Abilify Maintena, Aristada).

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